CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
FENTHION

Chemical Code # 63, Tolerance # 214
SB 950 # 040

October 1, 1986
Revised 2/27/87, 12/17/87, 8/4/88, 4/11/90, 4/9/92, 12/23/93, 10/20/95 and 12/2/97

DATA GAP STATUS

Chronic rat:	No data gap, possible adverse effect (not tumors)
Chronic dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effects
Reproduction, rat:	No data gap, possible adverse effect
Teratogenicity, rat:	No data gap, no adverse effect
Teratogenicity, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, possible adverse effect
Chromosome effects:	No data gap, possible adverse effects
DNA damage:	No data gap, possible adverse effect
Neurotoxicity:	No data gap, possible adverse effect[a]

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[a] An acute neurotoxicity study in the rat is on file.

Note, Toxicology one-liners are attached

In the one-liners below:
** indicates acceptable study
Bold face indicates possible adverse effect
File name: T971202
Revised by C. Aldous, 12/23/93, 10/20/95 and by J. Gee, 12/2/97

All records on file as of 12/2/97 for the above study types have been examined. This includes record numbers through 155670 (Document 214-117) plus some record numbers of the series

900000+.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may identify additional effects.

COMBINED, RAT

****214-097 098227** "Combined chronic toxicity/oncogenicity study of technical grade fenthion (Baytex®) with rats", (W. R. Christenson, Mobay Corporation, Study No. 87-271-01, 12/17/90), Mobay Report No. 100586. Fenthion technical, purity 97%, administered in the feed at nominal concentrations of 0 (Corn oil), 5, 20, or 100 ppm to 50 Fischer 344 rats/sex/group for 2 years. An additional 20/sex were treated at 0 and 100 ppm for 1 year as a satellite study. Cholinesterase inhibition NOEL < 5 ppm: brain ChE was inhibited significantly at all doses in both sexes; plasma ChE was clearly inhibited in all doses of females and at 20 ppm and above in males [and marginally (7-19%) in 5 ppm males]. RBC ChE was clearly inhibited at 20 ppm and marginally at 5 ppm in both sexes. NOEL (other than ChE enzyme inhibition) = 5 ppm [modest suppression of electroretinogram (ERG) in females, vacuolar degeneration of the nasolacrimal duct in females, and granulomatous pneumonia in males]. Prominent features at 100 ppm included: modest body weight decrements (both sexes); skin lesions of tail and hindlimbs (both sexes, considered chronic active inflammation); other signs of unthrifty animals including urine stained ventrum and rough coat (both sexes); ocular effects, including retinal atrophy and cataract formation (females), focal corneal scarring (both sexes), and atrophy of the optic nerve (elevated in both sexes, but definitively treatment-related in females only): some of these morphological changes were reflected in undetectable electroretinogram responses in 100 ppm females. Other findings at 100 ppm were respiratory changes, including vacuolar degeneration of the nasolacrimal duct, foreign material in the nasal passageway, and granulomatous pneumonia (all in both sexes); and mineralization of the muscularis externa of the stomach (both sexes). Effects on eyes, respiratory system, skin, and epididymides are considered **Possible adverse effects**. **No oncogenicity response**. Study is **acceptable**. Kishiyama and Aldous, 4/9/92. (See Record No. 122320 below, which did not change study acceptability status).

214-097 098228 Identity of test article for record # 098227, above.

214-103 122320 [Addendum to Document No. 214-097, Record No. 098227, Miles Report No. 100586-1] Supplementary data by Christenson, W.R., entitled "Supplemental submission to EPA MRID No. 41743101". New information is Miles Report No. 100586-2, produced at Miles Inc., Stilwell, Kansas, Feb. 2, 1993. This record addresses 5 questions posed by Health and Welfare, Canada regarding the rat combined study. No change in status of the study (acceptable, possible adverse effects: not oncogenicity). Responses are discussed in the DPR review. Aldous, 9/28/93.

214-102 122319 [Addendum to Document No. 214-097, Record No. 098227, Miles Report No. 100586]. Supplementary data by Christenson, W.R., entitled "Supplemental submission to EPA MRID No. 41743101". New information is Miles Report No. 100586-1, produced at Miles Inc., Stilwell, Kansas, 8/13/93. This submission provided body weights of all rats, recorded on a single day, showing comparable weights between groups. Errors in table headings indicating implausible "day of study" entries were explained. No change in status of the study (acceptable, possible adverse effects: not oncogenicity). Responses were discussed in the DPR review.

Aldous, 12/23/93.

CHRONIC TOXICITY, RAT

Note that a combined study has been accepted, and that study (097:098227, above) is the only acceptable or upgradeable study suitable for hazard assessment of chronic effects in rats (Aldous, 4/9/92).

041/051 011843, "Bay 29 493 (Fenthion) Chronic Toxicity Study on Rats (Two-year feeding experiment)", (Bayer, 5/17/77). Fenthion (97.9%) fed in the diet at 0, 3, 15 and 75 ppm to Wistar rats for 2 years; 50/sex/group in the test article groups, 100/sex in the control group; no onco effects reported, Cholinesterase inhibition NOEL = 3 ppm (plasma and RBC cholinesterase activities decreased at 15 and 75 ppm). Apparent general systematic NOEL = 15 ppm (significant body weight decrease in males at 75 ppm). UNACCEPTABLE (inadequate number of tissues examined for histopathology, no analysis of dosing material provided, insufficient blood chemistry data, test article not adequately characterized), NOT UPGRADEABLE. (J. Wong, 4/30/85).

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 1/24/89) notes EPA classification for study 041/051 011843 as "Core Supplementary".

048 024914, Partial duplicate of 041/051:11843.

214-010 038403 [also reported in 214-011 044474] Doull, J. et al., "Chronic Oral Toxicity of Bayer 29493 to Male and Female rats", (Univ. Chicago, 1/28/63). Brief summary. Fenthion (no purity indicated) fed in the diet at 0, 2, 3, 5, 25 and 100 ppm for 12 months to Sprague-Dawley rats; 25/sex/group; no adverse systemic or onco effects noted; Apparent cholinesterase inhibition NOEL = 3 ppm (serum and plasma cholinesterase slightly inhibited at 5 ppm and above, brain ChE at 25 ppm and above); Apparent systemic NOEL = 5 ppm (decreased survival of males at 25 and 100 ppm); UNACCEPTABLE (considerable intercurrent disease, no characterization of test article, no analysis of dosing material, inadequate number of animals, no hematology, urinalysis or blood chemistry data, several other variances from guidelines), NOT UPGRADEABLE. (J. Wong, 4/30/85).
NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 1/24/89) notes that EPA did not classify this study, however the study was not considered acceptable to support registration.

044 024935, "Acute and Chronic Toxicity of 75 Pesticides to Various Animal Species", (Published in Down to Earth, 35:25-31). Fenthion listed in a table comparing toxicity of 75 pesticides. No useful information.

214-044 024938 Shimamoto, K., and Hattori, K., "Chronic feeding of BAYTEX . . . in rats", 3/16/67. This is a subchronic study reported in a few pages, and limited to cholinesterase effects. No review necessary. Aldous, 3/12/92.

214-014 046404 Report has identical title and date, and is apparently identical to 044:024938, above. Aldous, 3/12/92.

CHRONIC TOXICITY, DOG

214-098 098292, "Chronic Feeding Toxicity Study of Fenthion Technical (Baytex®) with Dogs" (W.R. Christenson, Mobay Corporation Toxicology Department, Study No. 87-274-01, Mobay Report No. 94863, 7/31/90). Fenthion technical, purity 97.1%, administered at nominal concentrations of 0 (1% corn oil as vehicle and mixing aid), 2, 10 and 50 ppm to 4 beagle dogs/sex/group for one year. ChE inhibition NOEL = 2 ppm, based on plasma cholinesterase inhibition. NOEL for RBC and brain ChE = 10 ppm. There were no other definitive treatment effects. Originally classified as "not acceptable" (additional dose rationale information was requested). Later accepted on receipt of Record No. 124367, below. **No adverse effects. Kishiyama and Aldous, 4/9/92; Aldous, 12/23/93.

214-105 124367 [Addendum to Document No. 214-098, Record No. 098292, dog chronic study]. Author of addendum: Christenson, W.R. Title of addendum: "Supplemental submission to EPA MRID No. 416328-01". Miles Report # 94863-2. Addendum refers to a Miles Inc. study performed at Stilwell, Kansas. Addendum date: 6/28/93. This submission included U.S. EPA data review of the dog study, which classified the study as "Core Guideline". Also included was the associated correspondence between the registrant and U.S. EPA. This submission provided data from rodent studies, particularly cholinesterase tables, taken from studies previously submitted. This reviewer recommends that the dog chronic study be upgraded to **acceptable** status, based on (1) the noteworthy brain cholinesterase inhibition observed in the chronic dog study, (2) the relatively steep dose-response for cholinesterase inhibition in rodent studies at comparable dose levels, and (3) an acknowledgment that the acceptable rat combined study identified a variety of effects at 100 ppm, some of which were also noted at 20 ppm, making the rat combined study the principal basis for chronic effects evaluation. Aldous, 12/23/93.

214-101 122318 Christenson, W.R., [addendum to Document No. 214-098, Record No. 098292], "Supplemental submission to EPA MRID No. 41632801", Miles Report No. 94863-1, addendum dated Oct. 7, 1992. Clarifications of 3 points relating to the study were provided in response to Health and Welfare, Canada request. None of the responses impact study status at DPR. Aldous, 9/29/93.

043/049 010694, "Fenthion-Chronic Toxicity Study on Dogs (2-year feeding) (Lebaycid-Baytex)", (Bayer, 11/20/75). Fenthion, tech., fed in the diet at 0, 3, 10 and 30 (graduated to 60 between weeks 64 and 67) ppm for the balance of the 104 week study; 4/sex/group. Apparent systemic effects NOEL = 30 (changed to 60) ppm (highest dose tested). Apparent cholinesterase NOEL = 3 ppm: modest decrease in plasma and RBC cholinesterase activity at 10 ppm; 60 ppm group levels of RBC, plasma, and brain ChE at 104 week term were 29, 41, and 65% of controls. UNACCEPTABLE STUDY: (test article not characterized, no analysis of dosing material, no justification of dosing levels given, no individual animal data provided), STUDY NOT UPGRADEABLE. (J. Wong, 4/23/85).
[EPA one-liner: Systemic NOEL > 60 ppm, ChE inhibition NOEL = 3 ppm; CORE grade-supplementary.]

214-010 038404 Doull, J., "Chronic Oral Toxicity of Bayer 29493 to Male and Female Dogs (Fenthion)", (Univ. Chicago, 2/6/63). Fenthion (purity not stated) given in the diet at 0, 2, 5 and 50 ppm; 2/sex/group; no adverse effects reported; limited cholinesterase inhibition in RBC, plasma and brain; data inadequate for establishing a NOEL; UNACCEPTABLE (no characterization of test article, no analysis of dosing material, inadequate number of animals, other major variances from guidelines), NOT UPGRADEABLE. (J. Wong, 4/30/85).

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 1/24/89) notes that EPA did not classify this study, however the study was not considered acceptable to support registration

CHRONIC TOXICITY, MONKEY

052 026470, "Safety Evaluation of Fenthion (S1752) in Rhesus Monkeys (Macaca mulatta)", (Albany Medical College, 3/80). Test article = S1752 = tech. fenthion. Doses = 0, 0.02, 0.07, and 0.20 mg/kg daily in corn oil, by gavage. Cholinesterase inhibition NOEL = 0.07 mg/kg (modest decrements in female plasma ChE, typically approx 30%: Table III of report). General systemic NOEL = 0.20 mg/kg/day (no evidence of toxicity other than ChE inhibition). Not acceptable, not upgradeable: animals not necropsied; dose levels not justified, and no evidence that an MTD was considered in dose selection. No review generated other than this one-liner. (Aldous, 9/3/86).

043 010677, (Albany Med. College, 3/80). Summary and table of contents of 052:026470, above. (Tab 3.6.8.a)

ONCOGENICITY, RAT

NOTE: The data gap is filled by combined study 214-097 098227, above. The 1979 NCI study below is unlikely to be of value for risk assessment). Aldous, 4/9/92.

214-035/046 010693, "Bioassay of Fenthion for Possible Carcinogenicity", (NCI, 79). Fenthion (purity not indicated) fed in the diet at 0, 10 and 20 ppm to F344 rats for 24 months; 50/sex/ test article group, 25/sex in controls; inadequate data for determining potential adverse effects or NOEL; UNACCEPTABLE (test article not characterized, no analysis of dosing material, only two dosing levels, MTD not approached, other major variances from guidelines), NOT UPGRADEABLE. Original review by J. Wong, 4/25/85 indicated inadequate study with possible adverse effect (endometrial stromal polyps). Study re-reviewed by C. Aldous, 5/6/86, who concluded UNACCEPTABLE, with no adverse effects (insufficient evidence to substantiate a treatment effect).

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 1/24/89) notes EPA classification as "Core Supplementary".

214-035 908970 Duplicate record number for 043/035/046 010693, above.

ONCOGENICITY, MOUSE

NOTE: In addition to the following acceptable study, there are two unacceptable mouse oncogenicity studies listed in this section (Record Nos. 010693 and 026884). The latter study was listed as "Not upgradeable" by CDFA and as "Invalid" by U.S. EPA, thus it does not appear to be useful for further evaluation, despite an apparent increase in bronchogenic tumors in males in that study. The former study (Record No. 010693, a 1979 NCI study), was also classified as "Not upgradeable" by CDFA, but was considered "Supplementary" by U.S. EPA. The NCI study had determined that male mice had increased incidence of tumors of skin (particularly subcutaneous tissues). The more recent study (Record No. 098230) employed a slightly higher upper dose level than the NCI study, as well as larger group sizes. Both studies used the same strain of mice. The absence of tumor effects in the recent study supersedes

findings of either of the older studies. Aldous, 10/7/93: updated by Aldous, 10/20/95.

214-096 098230 Leser, K.H., and Suberg, H., "E 1752: Oncogenicity study on B6C3F1 mice (Feeding study for periods up to 24 months)". (Bayer AG, Fachbereich Toxikologie, Wuppertal; Bayer AG Report No. 19624, Mobay Report No. 100581, 10/25/90). E 1752 [= fenthion] purity 98.2%-98.7%, admixed with the feed at concentrations of 0, 0.1, 1, 5, and 25 ppm to 60 (main group) plus 20 (50-wk interim sacrifice) B6C3F1 mice/sex/group for up to 102 weeks. Cholinesterase inhibition NOEL = 0.1 ppm/day (based on plasma cholinesterase inhibition). NOEL for findings other than ChE inhibition = 5 ppm [slight cholesterol elevation at 25 ppm at 28 or 54 weeks (F) and at 28 weeks (M)]. This study had been classified as unacceptable in the 1992 review. Subsequently, records 125488 and 125506 were submitted in support of dose level selection for the primary study. These were two 4-5 week studies in mice, exposed to dose levels of 50 to 250 ppm in diet. The essential information from these studies included marked brain cholinesterase inhibition in both sexes (60-61% at 50 ppm); plus emaciation, tremors, and mortalities in males at 150 ppm and above. The latter records were classified unacceptable in the 1993 DPR reviews, primarily due to lack of verification of dose levels administered. Records #131635 and #131637 provided data to upgrade the two 4-5 week studies. The toxicity profiles (including brain cholinesterase effects) of these latter studies suffice to justify dose levels selected for the primary study, which is now re-classified as **acceptable. **No adverse effect is indicated**. (Kishiyama and Aldous, 4/9/92; Aldous, 10/20/95).

214-106 125488 Leser, K.H., "Study for cholinesterase inhibition following high doses of E 1752 (Administration to B6C3F1 mice in the diet over a period of about four weeks)", Miles Report No. 101930, Bayer AG, Wuppertal, 5/28/90. [This study relates to Record No. 098230, above.] This ancillary study was originally considered unacceptable in support of the primary oncogenicity study (Record # 098230, above). Later information in Record # 131635 (below) make this study **acceptable**. E 1752 (Fenthion), 98.7%, was administered in diets of 10 mice/sex/group at nominal levels of 0, 150, 200, or 250 ppm for "about 4 weeks". Parameters included body weights, food intake, clinical observations, cholinesterase activities, and gross necropsy exams. Purpose of study was to examine treatment effects in a range which would establish an "MTD". "Emaciation" was noted for all treated males and for most treated 250 ppm females during the first week. "Emaciation" was rarely noted after week 2. The majority of males in all groups had tremors during the first week, continuing into week 2 for many 200-250 ppm males. Females did not show tremors. Three 250 ppm males and two 200 ppm males died spontaneously or were killed moribund on study. Of the remaining 25 treated males, 18 died during routine extra-orbital blood sampling near end of study. This was considered treatment-related. Body weights fell sharply in all treated groups at week 1, with slow recovery for all groups. Food consumption was not affected. Plasma cholinesterase inhibition was 98-99% for all groups, and blood cholinesterase was inhibited at least 93% in males and at least 80% in females at these dosages. Brain cholinesterase inhibition ranged 73 to 80% for males and 68 to 73% for females. Insulin levels were elevated in treated males and females, sometimes statistically significantly, suggestive of an altered pattern of carbohydrate metabolism. Items considered inadequate in the original report were (1) deviations of this study with respect to published guidelines needed to be specified, (2) laboratory records of diet preparation were required, and (3) individual brain cholinesterase data were required. These items were addressed in the record immediately below. Aldous, 10/6/93 and 10/20/95.

214-109 131635 [addendum to Document No. 214-106, Record No. 125488] Leser, K.H., "Study for cholinesterase inhibition following high doses of E 1752 (Administration in feed over 4 weeks to B6C3F1 mice)", Bayer AG Institute of Industrial Toxicology, Germany. Date of the supplement: Aug. 1, 1994. Miles Report #101930-1. (1) Report acknowledged that there was

no QA oversight of the study, and that stability,
homogeneity, and content of the test article were not measured in the study. (2) Laboratory protocols for diet preparation and contemporary records of weighed amounts of feed, mixing aid (peanut oil), and test article were provided. (3) Individual brain cholinesterase data were provided. Thus supplementary data provide sufficient information to make the range-finding study **acceptable**, since diet preparation records were clear and appropriate for intended dose levels, and individual brain cholinesterase data verified that high levels of inhibition were achieved. Aldous, 10/20/95.

214-107 125506 Leser, K.H., "E 1752 Technical (Common Name: Fenthion): Range-finding study to determine the maximum tolerated dose (MTD) of B6C3F1 mice (Administration in the feed for up to 5 weeks)", Bayer AG, Wuppertal, 4/21/89. Miles Report No. 99653. This ancillary study was originally considered unacceptable in support of the primary oncogenicity study (Record # 098230, above). Later information in Record # 131637 (below) make this study **acceptable**. E 1752 (Fenthion), 98.7%, was administered in diets of 10 mice/sex/group at nominal levels of 0, 50, 75, or 100 ppm for 5 weeks. Parameters included body weights, food intake, clinical observations, cholinesterase activities, and gross necropsy examinations. Purpose of study was to examine treatment effects in a range which would establish an "MTD". Body weight gains were reduced in 75-100 ppm males during week 1. There were no other b.w. changes, nor clinical signs. Inhibition of cholinesterase was as follows: 96-98% for plasma, 88-100% for RBC, and 57-69% for brain: there was no apparent sex difference in inhibition, nor was there a perceptible dose-response over this range for brain cholinesterase inhibition. Study, as supplemented by diet preparation data in Record No. 131637 (below), is useful in justifying dose levels used in the mouse oncogenicity study. Aldous, 12/23/93 and 10/20/95.

214-110 131637 [addendum to Document No. 214-107, Record No. 125506] Leser, K.H., "Range-finding study to determine the maximum tolerated dose (MTD) of B6C3F1 mice (Administration in feed for up to 5 weeks)", Bayer AG Institute of Industrial Toxicology, Germany. Date of the supplement: Aug. 1, 1994. Miles Report #99653-1. This report acknowledged that there was no QA oversight of the study, and that stability, homogeneity, and content of the test article were not measured in the study. Laboratory protocols for diet preparation and appropriate contemporary records of weighed amounts of feed, mixing aid (peanut oil), and test article were provided. This supplementary report is virtually identical to Record No. 131635, which was submitted in support of Record No. 125488, except that this supplementary report did not include individual brain cholinesterase data (which were not requested upon initial review of Record No. 125506). These supplementary data provide sufficient information to upgrade the range-finding study to **acceptable** status. Aldous, 10/20/95.

214-104 122794 Leser, K.H. and Sunberg, H., "E 1752: Oncogenicity study on B6C3F1 mice (Feeding study for periods of up to 24 months)". Miles Report No. 100581-1. This submission addressed two issues raised by Health and Welfare, Canada regarding the mouse study (Record No. 098230, above). Items were not at issue at DPR, and no DPR worksheet is needed. Aldous, 10/6/93.

214-105 124368 [Miles Report No. 100581-2] Van Goethem, D.L, and Leser, K.H., (submission regarding the mouse study: Record No. 098230, above). Record is primarily an overall summary of the preceding two 4-5 week high-dose mouse feeding studies, plus the U.S. EPA data review of Record No. 098230. The U.S. EPA review classified the study as "Core Guideline". No DPR worksheet is provided, since the data are not unique to this record. DPR objections to the admissibility of the short-term study data are detailed in the respective reviews or 1-liners. Aldous, Oct. 7, 1993.

043/035/046 010693, "Bioassay of Fenthion for Possible Carcinogenicity", (NCI, 79). Fenthion (purity not stated) fed in the diet at 0, 10 and 20 ppm to B6C3F1 mice for 24 months; 50/sex/test article group, 25/sex in control group; No apparent NOEL: Sarcomas of skin and subcutaneous tissues may be treatment related: a **possible adverse effect**. UNACCEPTABLE (test article not characterized, no analysis of dosing material, only two dosing levels, MTD not approached, other major variances from guidelines), NOT UPGRADEABLE. (J. Wong, 4/25/85). [NOTE: see beginning of mouse oncogenicity section.]

EPA one-liner: "Fenthion was not carcinogenic for female mice under the test conditions. Male mice developed sarcomas but at a rate not significantly higher than untreated control mice." (report not "core- graded" by EPA, as of 4/86 EPA One-liners.) NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 1/24/89) notes EPA classification as "Core Supplementary".

054-055 026884-5, "Tumorigenic Study of Fenthion in Mice (Volume I of II)", (Albany Med. School, 12/80). Fenthion (98.1%) fed in the diet at 0, 1, 5 and 25 ppm for 21 months to CD-1 mice; 80/sex/group at low and mid dose levels, 120/sex/group at high dose and in control group; Apparent general systemic NOEL = 25 ppm (HDT). No apparent cholinesterase inhibition NOEL: slight but statistically significant decrease in plasma ChE in females as low as 1 ppm (lowest dose tested) for first 26 weeks of study. No apparent effects of ChE inhibition nor other general appearance or behavioral manifestations of toxicity. **Possible significant oncogenic effect:** increased frequency of bronchogenic carcinomas and adenomas in males at the high dose; UNACCEPTABLE (no analysis of dosing material, no justification of dose levels with respect to MTD, incomplete histopathology, excessive mortality), NOT UPGRADEABLE. (Aldous, 9/11/85). NOTE: This study was re-examined by Aldous on 4/11/90. The study acceptability status is unchanged (unacceptable). [NOTE: see beginning of mouse oncogenicity section.]

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 1/24/89) notes EPA classification as "Invalid".

043/044 010695, Less complete version of record #s 26884-26885.

044 024934, Abstract/analysis of study: record #s 26884-26885.

REPRODUCTION, RAT

****214-093 090460** Kowalski, R.L., Clemens, G.R., Jasty, V., Troup, C.M., and Hartnagel, R.E., "A Two-Generation Reproduction Study with Fenthion (BAYTEX) in the Rat", (Miles Inc., Report No. 99811, 12/22/89). Fenthion, 96.9%, Batch #85R0146I, was administered in the diet to groups of 30 rats/sex continuously from 10 weeks prior to initial mating through 2 generations, 1 litter per generation, at doses of 0 (vehicle control), 1, 2, 14, and 100 ppm (0, 0.08, 0.16, 1.12, and 8.0 mg/kg/day, respectively). Epididymal cytoplasmic vacuolation (ECV) associated with decreased fertility occurred in 7 and 100% of the 14 and 100 ppm males respectively. At 100 ppm, fertility indices were decreased, and peri/postnatal death and postnatal growth retardation were increased. Reproductive NOEL = 2 ppm (ECV associated decreased fertility); ChE inhibition NOEL = 2 ppm; ChE inhibition NOAEL > 100 ppm. The study is ACCEPTABLE, and the **POSSIBLE ADVERSE HEALTH EFFECTS** of ECV associated decreased fertility, reduced survivability, and postnatal growth retardation, are noted (G. Chernoff, 3/30/90).

043/014 010691, "Bay 29493 (Technical) generation tests on rats (F1, F2, F3, Reproduction Study)-Baytex", (Bayer, 5/2/69). Fenthion (purity not stated) fed in the diet at 0, 3, 15 and 75

ppm for a 3 generation, 2 litters/generation study; 10 males and 20 females/group; insufficient information for assessment of potential adverse effects and for establishing NOEL; UNACCEPTABLE (test article not characterized, no analysis of dosing material, no justification of dosing levels, inadequate number of animals, inadequate necropsy and histopathology data), NOT UPGRADEABLE. (J. Wong, 4/16/85). (Reviewed by J. Parker, 3/14/86).
EPA one-liner: Need raw data; CORE grade - supplementary.

047 024918 Partial duplicate of record #10691.

TERATOGENICITY, RAT

**081 061601 & 083 063390, "A Teratology Study with Fenthion (Baytex® Technical) in the Rat", (Miles Laboratories, Inc., 8/26/87). Fenthion, Batch No. 85R-01-46I, 96.5% a.i.). 0, 1, 4.2, and 18 mg/kg/day via aq. Emulphor gavage to Crl:CD®BR females on days 6-15 of gestation. Maternal NOEL (excluding ChE inhibition) = 4.2 mg/kg/day (diminished weight gain and cholinergic signs). Maternal ChE inhibition observed in all treatment groups in a dose-related manner. Developmental NOEL = 4.2 mg/kg/day (marginal increase in resorptions at 18 mg/kg/day). Study ACCEPTABLE, with no adverse effects. (C. Aldous, 12/17/87).

043/047 010689, "Evaluation for Embryotoxic and Teratogenic Effects in Orally Dosed Rats (Lebaycid-Baytex)", (Bayer, 6/7/78). Fenthion (purity not indicated) given by oral gavage at 0, 1, 3, and 10 mg/kg/day on days 6-15 of gestation to FB 30 Long Evans rats; 19-20/group; no indication of any maternal or developmental toxicity; apparent maternal and developmental NOEL=10 mg/kg; UNACCEPTABLE (test article not characterized, no analysis of dosing solution, MTD not achieved, individual animal data not included, no necropsy or clinical observations), NOT UPGRADEABLE. (J. Wong, 4/26/85).

TERATOLOGY, RABBIT

043/047 010688, "Embryotoxicity and Teratogenicity Study on S 1752 in Rabbits (Baytex)", (Res. & Consulting Co., Ltd.-11/18/82). Fenthion, tech. given by oral gavage at 0, 2, 6 and 18 mg/kg/day on days 6-18 of gestation; severe maternal toxicity at 18 mg/kg, increased resorptions at mid dose level; maternal NOEL = 6 mg/kg/day (death and body weight decrease). **Possible adverse effect**: developmental NOEL = 2 mg/kg/day (fetal death). J. Wong, 4/29/85, noted study was UNACCEPTABLE, with parental and reproductive effects. Study was re-examined by J. Parker, 2/5/86 (no separate written review), who noted that study was UPGRADEABLE: (attachment 3 illegible - reissue, needs individual clinical observations, needs individual fetal data for all exams)
EPA one-liner: Maternal NOEL= 6 mg/kg/day, teratogenic NOEL > 18 mg/kg/day, fetotoxic NOEL = 2 mg/kg/day; CORE grade - minimum.

**084 065024, "A Teratology Study in the Rabbit with Fenthion (Baytex Technical)", (Miles Inc., Toxicology Department, Elkhart, IN, report no. MTD0039, 12/7, 1987). Fenthion (batch no. 85R-01-46I, purity 96.5%) administered by gavage to 17 American Dutch rabbits/group at doses of 0 (5% Emulphor), 1, 2.75 or 7.50 mg/kg once daily from the sixth through eighteenth day of gestation. Inhibition of plasma and erythrocyte (RBC) cholinesterase activity (>20%) and brain cholinesterase for mid and high dose groups. No overt cageside observations relative to cholinesterase inhibition reported. The incidence of soft stools for mid and high dose groups increased 35% and 71%, respectively; also, slight reduction of body weight gain, in addition to a trend towards lower food consumption for mid and high dosage. Maternal NOEL = 1 mg/kg/day.

External and visceral fetal malformations were comparable to the control. Total resorptions and number of does with more than 1 resorption and increased incidence of unossified metacarpals was associated for the 7.5 mg/kg/day group - developmental NOEL = 2.75 mg/kg/day. No adverse effect. ACCEPTABLE. (J. Parker and J. Kishiyama, 7/15/88).

Summary: A recent acceptable study (#065024) measured cholinesterase depression in the dams and found significant depression in plasma, RBC and brain cholinesterase at levels (2.75 and 7.5 mg/kg/day) below that eliciting developmental toxicity (7.5 mg/kg/day). No adverse effect was noted in this study. However, an earlier unacceptable study, (#010688) indicated a possible adverse effect since the developmental NOEL (2.0 mg/kg/day) was less than the maternal NOEL (6.0 mg/kg/day). It is likely that this study would have had a lower maternal NOEL had cholinesterase depression been measured.
Therefore, the conclusion of this reviewer is that there is no indication of an adverse developmental effect following fenthion administration to rabbits. (Parker, 7-15-88).

TERATOLOGY, MOUSE

043/047 010690, "Teratogenicity and Embryotoxicity of Demeton and Fenthion in CF #1 Mouse Embryos", (Univ. West. Ontario, 73--Journal article). Fenthion (purity not indicated) administered by i.p. injection of 0, 20, 40, or 80 mg/kg to pregnant mice on a single day or on 3 consecutive days; no data presented; insufficient information for evaluation; UNACCEPTABLE (major variations from guidelines), NOT UPGRADEABLE. Original review by J. Wong, 4/25/85, indicated possible adverse effect (embryo/fetotoxicity). Re-examination by J. Parker (3/14/86) noted maternal toxicity at same dose levels which caused developmental toxicity, hence no adverse effect is indicated.

GENE MUTATION

043/045 010687, "Salmonella/Microsome Test for Detection of Point-Mutagenic Effects (Lebaycid-Baytex)- Ames Test", (Bayer, 4/16/80). Fenthion (98.5/98.7%) tested at 6 levels between 217.5 to 12,500 ug/plate +/- S9 on Salmonella strains TA100 and TA1535; 4 replicates/level, 3 levels of S9 mix tested, repeat trial; precipitation at 3000 ug and above; no reproducible increase in mutation frequency with test article; UNACCEPTABLE (only 2 strains used, individual plate counts not presented), NOT UPGRADEABLE. (J. Wong, 4/29/85).

045 024924, Review article by D. Brusick et al.. Contains 1-line reference to 080:060687, already reviewed by CDFA. No further information needed.

043 010682, "Ames Test for Lebaycid-Baytex", (Lab ???, 10/25/77). Fenthion (98.1/97.5%) tested at 0 to 3150 ug/plate +/- S9 on Salmonella strains TA 1537, TA98 and TA100; no increase in mutation frequency with test article; UNACCEPTABLE (no repeat trial, strain TA1535 not included), NOT UPGRADEABLE. (J. Wong, 4/29/85). (Reviewed by J. Remsen, 1/4/86).

043/045 010684, "Fenthion: Mutagenicity Test on Bacterial Systems: Reversion Assay, Salmonella Typhimurium", (Nitokuno Ag. Chem. Inst.-Japan, 7/1/76). Fenthion (96.1%) tested at 0, 0.1, 10 and 1000 ug/plate +/- S9 (rat and mouse) on Salmonella strains TA98, TA100, TA1535 and TA1537; marginally (2-3 fold) increased reversion rate at high concentration only with S9 in TA1535 with both rat and mouse activation; UNACCEPTABLE (no justification of dose levels, no indication of number of platings nor number of repeats indicated, no individual data, no minus activation). (J. Wong, 4/29/85 and J. Gee, 12/14/87).

043 038408, 038409, "Report of the Mutagenicity Study of Fenthion," (Inst. Env. Tox.-Mobay, 1/25/79). Fenthion (95.7%) tested at 0, 10, 50, 100, 500, 1000 and 5000 ug/plate +/- S9 on Salmonella strains TA1535 (4 trials - increase with S9 was noted in three of the trials), TA1537, TA1538, TA98 and TA100, also E. coli WP hcr$^-$; marginal increase in revertants with TA1535, +S9; ACCEPTABLE for Salmonella assay only. (J. Wong, 4/29/85). (Reviewed by Remsen, 1/4/86).

043/045 010686, "Mutagenicity Screening of Pesticides in the Microbial System", (Natl. Inst. Genetics-Japan, 76, published in Mutation Research 40: 19 - 30, (1976), Shirasu et al.) Both Salmonella strains (TA1535, TA1536, TA1537 and TA1538) and Escherichia coli strain wp2 were tested. Summary only; survey of results with 166 pesticides screened in Ames test; no data; no adverse effects reported; UNACCEPTABLE. (J. Wong, 4/29/85).

043/045 010685 [same as 214-045 024933] "Mutagenic Effect of Pesticides on Escherichia coli WP2 Try-Minus (Fenthion)", (Bioch. Inst.-Budapest, 75, published in Acta Microbiol. Acad. Sci. hung. 22: 309 - 314 (1975), Nagy et al.) Summary only; survey of testing 30 pesticides on E. coli WP 2; no data, no adverse effects reported; UNACCEPTABLE. (J. Wong, 4/19/85).

038 017654, "Mutagenicity of Organophosphorus Compounds in Bacteria and Drosophila", (Article by Hanna and Dyer, Mutation Res. 28: 405-420, 1975). Fenthion was negative in preliminary tests with S. typhimurium and E. coli. No individual data. Tiered testing - compounds negative in bacteria were not tested in Drosophila - fenthion was negative in bacteria. UNACCEPTABLE, no adverse effects indicated. No further information requested. (C. Aldous, 12/11/87). (no written CDFA review).

Summary: In the three reports with data, the responses with Salmonella TA1535 were reviewed as marginally positive in two and considered negative in a third study (034/045:10687). The data in the latter study are suggestive of a weak response with TA1535, however not statistically significant. No increase in reversion rate was seen with any other strain or with E. coli. The increases were 2 - 3 fold and were not well-correlated with increasing concentration. The significance of this finding in TA1535 is equivocal but the possible adverse effect remains because of the consistency of the effect. An acceptable study in mammalian cells would assist in determining the biological significance of the effect noted in one strain of one species of bacteria. (J. Gee, 12/14/87).

CHROMOSOME EFFECTS

** 094 088647, "Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells", (D. L. Putman and M. J. Morris, Microbiological Associates, Inc., Laboratory Study Number T8301.337, Mobay report 99660, July 27, 1989). Baytex technical, purity 97.1%, was assayed at concentrations of 0.02, 0.04, 0.08, or 0.15 ul/ml of medium without and with a metabolic activation (S-9 Mix) from male rat. Dose selection for the chromosome aberration assay was limited by solubility of Baytex in the medium. The study includes an untreated control, vehicle control (DMSO) and positive controls: Triethylenemelamine (TEM) and Cyclophosphamide (CP). Exposure time was 18 and 2 hours for treatments without and with metabolic activation, respectively. Reduced mitotic indices and slight toxicity were associated with Baytex treatments. The number of chromosome aberrations was not increased with Baytex treatments. ACCEPTABLE with no indication of an adverse effect. (Kishiyama and Gee, 4/6/92.)

043 010681, "Dominant Lethal Study on Male Mice to Test for Mutagenic Effects (S 1752 Lebaycid-Baytex)", (Bayer, 4/10/78). Fenthion (98.1%) tested at 10 and 25 mg/kg in a single

dose by oral gavage with NMRI mice for a dominant lethal assay; 50 males/group; mated 1:1 for 12 periods; no adverse effects reported; UNACCEPTABLE (no positive controls included, only two dosing levels, no justification of dosing levels, inadequate description of methods for determining mating, tables not translated from German), insufficient information, PROBABLY NOT UPGRADEABLE. (J. Wong, 4/29/85 and J. Gee, 12/14/87). Discussed in 12/18/89 CDFA response to EPA memo of 1/24/89, which discussed data gap status of several studies.
NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 1/24/89) notes EPA classification as "acceptable".

043 010680 & 045 024930, "Micronucleus Test on Mouse to Evaluate S-1752 for Mutagenic Potential", (Bayer, 11/26/80). Fenthion (98.5-98.5%) tested at 0, 50 and 100 mg/kg/day by oral gavage on NMRI/W77 mice for a micronucleus assay; 2 doses, 24 hrs apart; single sampling time, 30 hrs after first dosing; 5/sex/group, 1000 polychromatic erythrocytes/mouse; no adverse effects reported; UNACCEPTABLE (only 2 dosing levels, only a single sampling time, inappropriate statistics - sexes analyzed together), NOT UPGRADEABLE. (J. Wong, 4/30/85).
NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 1/24/89) notes EPA classification of study 043 010680 & 045 024930 as "acceptable".

50615-001 052060 (Historical data for negative controls in micronucleus tests with cremophor suspensions).

045 024920, 024921, "Sister-Chromatid Exchanges and Cell-Cycle Delay in Chinese Hamster V79 Cells Treated with 9 Organophosphorus Compounds (8 pesticides and 1 defoliant)" and "Sister Chromatid Exchanges in Chinese Hamster Cells Treated with Seventeen Organophosphorus Compounds in the Presence of a Metabolic Activation System", (Roswell Park Mem. Inst., 24920 Mutation Research 103: 307-313, 1982 and 24921 Environmental Mutagenesis 4: 621-624, 1982, respectively). Fenthion (97.2%) tested at 0, 10, 20, 40 and 80 ug/ml on Chinese hamster cells (V79) in SCE assay with (24921) and without (24920) activation; 100 metaphases/dose level analyzed; without activation, a cell cycle delay and SCE/cell showed dose-dependent effect - most of cells at 80 ug/ml were in M1 (92%) at 27 hrs, therefore, should have harvested cells at a second time interval; in the presence of S9 activation, SCE/cell were also increased in a concentration-dependent manner. UNACCEPTABLE, NOT UPGRADEABLE. (Remsen (Gee), 9/19/85).

Summary: A **possible adverse effect** has been identified in an in vitro assay whereas two in vivo tests were negative. A recent publication by E. D. Thompson in Mutation Research 8: 753 (1986) compared the results in vitro for cytogenetics with in vivo results for cytogenetics or micronucleus formation for 216 chemicals. He concluded that 97% of the in vivo clastogens are positive in vitro but that the in vitro tests have a high incidence of "false positives" and a positive effect should be confirmed in animal studies. The author, however, did not use the stringent criteria of EPA's Gene-Tox reports so the adequacy of each of the studies was not addressed. Also, there is no assurance that the bone marrow is a target tissue. The dominant lethal test is a comparatively insensitive test even when conducted by suggested guidelines, as the one with fenthion was not. The **possible adverse effect** remains, based on the sister chromatid exchange studies. Gee. An additional negative in vitro assay is now on file but the endpoint is different from the positive SCE study. The conclusion remains the same. Gee, 4/7/92.

DNA DAMAGE

**** 095 098229**, "E 1752, c.n. Fenthion: Mutagenicity Test on Unscheduled DNA Synthesis in

Rat Liver Primary Cell Cultures In Vitro", (H. Lehn, Bayer AG, Institute of Toxicology, Report no. 19604, Laboratory Project ID 100572, Study No. T 7032949, 10/9/90). E 1752, purity 98.5/98.3%, was assayed at concentrations of 0 (DMSO), 5.0, 7.5, 10.0, 15.0, or 30.0 ug/ml. Exposure time was for 23 hours. The activity of fenthion in the UDS assay was indicated by marginal increases in nuclear grain counts (1.11 to 4.73) and a dose related trend for an increase in the number of cells in repair (6% to 48%). Fenthion at 7.5 ug/ml (during the repeat trial) was the only dose level that did not show an increase in either nuclear grain count or cells in repair. The two highest concentrations and the lowest (in both studies) had increases of both nuclear grain counts and cells in repair. Possible adverse effect. ACCEPTABLE. (Kishiyama and Gee, 4/6/92)

043/045 010683, 045 024926 "Report of the Mutagenicity Study of Fenthion", (Inst. Env. Tox.-Mobay, 1/25/79). Fenthion (94.7%) tested at 0, 1, 5, 10, 25 and 100% (v/v) in 0.02 ml in disk assay on B. subtilis strains H17 and M45; no adverse effects reported; UNACCEPTABLE (no individual data, no metabolic activation, no justification of dosing levels, other major variances from guidelines), NOT UPGRADEABLE. (J. Wong, 4/29/85).

043 038407, "Fenthion: Mutagenicity Test in Bacterial Systems", (Nitokuno Ag. Chem. Inst.-Japan, 7/1/76). Fenthion (96.1%) tested at 0, 3, 30 and 300 ug/disc on B. subtilis strains NIG 17 (rec^+) and NIG 45 (rec^-); no adverse effects noted; UNACCEPTABLE (number of plates not indicated, no negative control indicated, no justification of dosing levels, no activation included, incomplete protocol, methods of statistical analysis not indicated), NOT UPGRADEABLE. (J. Wong, 4/29/85 and J. Gee, 12/14/87).

043 038406, "Mutagenicity Screening of Pesticides in the Microbial System", (Natl. Inst. Genetics-Japan, 76, Shirasu et al., published in Mutation Research 40: 19-30, 1976). Summary only; no data, screening of 166 pesticides using the rec assay with B. subtilis; no adverse effects reported; UNACCEPTABLE. (J. Wong, 4/29/85).

056 030908, "E 1752 (Fenthion, Lebaycid and Baytex active ingredient) - Pol Test on E. coli to evaluate for potential DNA damage", (Bayer, 7/11/83). Fenthion (98.6%) tested at 0, 625, 1250, 2500, 5000 and 10,000 ug/plate +/- S9 on E. coli (p3478, W3110); 2 platings/dose level; UNACCEPTABLE (protocol incomplete, individual data not presented, lack of cytotoxicity makes this a "no test"), NOT UPGRADEABLE. (Remsen (Gee) 9/6/85 and 12/14/87).

045 024925, Near duplicate of record #30908 (same report, different format).

045 024922, Abstract on effects of several pesticides on mitotic gene conversion; no data; no adverse effect reported; UNACCEPTABLE.

080 060687, "Evaluation of Selected Pesticides as Chemical Mutagens in vitro and in vivo Studies", (Stanford Research Institute, 5/77, for U. S. EPA, Report 90892). Fenthion, 96.0%; tested with Saccharomyces cerevisiae D3 for mitotic recombination study in two trials (number of plates not given) with and without activation at 0 or 5% (w/v); no cytotoxicity and no significant increase in recombinants at 5% reported; insufficient information for an independent assessment; UNACCEPTABLE (incomplete report with no methods - only one page of data, number of plates not indicated, no justification for using 5%, single concentration, incubation time not indicated). Full report should be submitted. (J. Gee, 11/19/87).

080 060687, "Evaluation of Selected Pesticides as Chemical Mutagens in vitro and in vivo Studies", (Stanford Research Institute, 5/77, for U. S. EPA, Report 90892). Fenthion, 96.0%; unscheduled DNA synthesis study in WI-38 without activation at 0 (ethanol), 10^{-6}, 10^{-5}, 10^{-4}, 10^{-3}

M (6 samples per concentration) and with activation at 0, 10^{-5}, 10^{-4}, or 10^{-3} M (3 samples per concentration); no increase in dpm/ug DNA with or without activation. UNACCEPTABLE (incomplete report with no methods, only two tables of data). Full report should be submitted with details of DNA extraction, conversion of cpm to dpm, amount of DNA per flask. (J. Gee, 11/19/87).

045 024923, (1-paragraph abstract of SRI studies, presumed to include work reported in fuller detail in 080:60687, see above-2 entries).

Summary: A series of in vitro tests have been conducted measuring several different genotoxic endpoints. The three tests (10683, 34807 and 30908) comparing repair- proficient with repair-defective bacterial strains had major faults: there was no activation included in #10683 and #34807, and no evidence of diffusion nor cytotoxicity in any of the three studies. For these reasons, the three studies are not acceptable individually nor collectively. The two studies conducted at Stanford Research Institute with yeast and WI-38 would need to be submitted in full if an evaluation is desired. (J. Gee, 12/14/87). An acceptable study assaying for unscheduled DNA synthesis has been evaluated as indicating a positive finding. This fills the data gap as now constituted for DNA damage (Gee, 4/7/92).

NEUROTOXICITY

NOTE: The 1988 Mobay study (089:070783, below) was flagged as indicating a "possible adverse effect", based principally on lack of a NOEL for cholinesterase inhibition. Dr. Patterson noted also a decreased motor activity and ataxia, and microscopic neuronal lesions (lymphocytic accumulations, but not lesions of the type associated with classic organophosphorous chemical delayed distal neuropathies. Aldous, 4/9/92.

**** 089 70783**, "Subchronic Delayed Neurotoxicity Study of Fenthion Technical (Baytex*) with Hens"; Mobay Corp. E.H.&S. Report #98296; 82-5; 9/27/88; Fenthion technical (96.5% purity, Batch # 85-R-0146-I, CAS # 55-38-9) administered daily by oral gavage for 90 days to 10 hens/group at analyzed concentrations of 0.84, 1.7, and 3.2 mg/kg in corn oil (nominal concentrations were 1, 2, and 4 mg/kg, respectively), negative controls were 20 hens gavaged with corn oil only daily, positive controls were 10 hens gavaged daily with TOCP in corn oil with dose of 10 mg/kg increasing with time to 60 mg/kg; no mortalities in negative control or in 0.84 and 1.7 mg/kg groups, 30% in 3.2 mg/kg group, all TOCP-treated hens dead by day 78; feed consumption slightly decreased in 1.7 mg/kg group and decreased significantly in the 3.2 mg/kg group; mean body weights significantly lower in the 3.2 mg/kg group; decreased activity observed in 4/10 hens at 1.7 mg/kg and all hens at 3.2 mg/kg showed decreased activity and ataxia; statistically significant decrease in whole blood ChE values for all fenthion treated groups (48-64% from control) from week 2 through end of study; histoneuropathic findings in 1.7 and 3.2 mg/kg groups (e.g. lymphocyte accumulation) not indicative of TOCP-type induced delayed neuropathy (eg. axonal degeneration, demyelination); G.I. tract muscular hypertrophy and hyperplasia reported for hens in 1.7 mg/kg and 3.2 mg/kg groups; NOEL (Delayed Neuropathy) > 3.2 mg/kg, NOEL (Blood ChE) < 0.84 mg/kg; **Acceptable**. (Patterson, 4/28/89)

**063 050554, "Acute Neurotoxicity Studies on Hens Following Oral and Dermal Administration", (Fachbereich Toxikologie, Bayer AG, 9/22/86, (Bayer Report #15088, [Mobay #91341]). E 1752 = Fenthion technical, 94.2-98.5% purity, given at 40 mg/kg orally or 200 mg/kg dermally, to 15 white leghorn hens/group, with (6) atropine sulfate injections at intervals for protection. A second administration was given surviving animals after 21 days, with similar atropine protection. Substantial mortality in dermally-treated group, but there were enough survivors in all groups for

a meaningful test. Lethargy and staggering gait were observed for several days after oral or dermal application of fenthion, however symptoms were clearly reversible and pattern and degree of clinical signs did not resemble TOCP-type effects for either oral or dermal-dosed hens. Histopathology did not indicate TOCP-type microscopic lesions. Test article apparently does not cause delayed distal neuropathy. Two reviews by C. Aldous: study classified "Unacceptable" due to lack of QA signature page in 2/27/87 review, but ACCEPTABLE in 11/13/87 review with inclusion of QA signature page in the more complete version of the report (076 058068).

076 058068, complete version of 063 050554.

063 050553, (Dermal exposure study. No written review deemed appropriate.)

043 010679, "Neurotoxicity Studies on Hens-Histopathology Bay 29493 (Baytex)", (Bayer, 4/29/71). Fenthion (purity not indicated) given in the diet for 30 days at 0, 10, 25, 50 and 100 ppm; 8 hens/group; no adverse effects reported; UNACCEPTABLE (insufficient protocol, no justification for route of administration, no atropine prophylaxis, no positive controls, no characterization of test article, no analysis of dosing material), NOT UPGRADEABLE. (J. Wong, 4/30/85).

014 908920, Partial duplicate of 10679.

057 031889, Histopathology for record #10679.

010 038402, "Testing of the Neurotoxicity of S 1752 (Fenthion) for Hens", (Lab not indicated, 12/62). Summary only; Fenthion (no purity indicated) tested at 0.02 (14 hens), 0.025 (4 hens), 0.05 (2 hens) and 0.1 (2 hens) g/kg; no adverse effect reported; UNACCEPTABLE (only highest dose approached adequate level, no forced motor activity, no positive controls, no histological exams on hens, no individual data presented, no second dose administered), NOT UPGRADEABLE. (J. Wong, 4/30/85).

057/044 031888, "Neurotoxicity Studies with Bay 29493 - Hens", (Bayer, 5/20/65). Summary only; Fenthion (50%) given in the diet at 0, 300, 1000, 3000 and 10,000 ppm for 38 days; insufficient data to evaluate; no adverse effect.

214-043 010678 Kimmerle, G. and Lo"ser, E., "Delayed neurotoxicity of organophosphorus compounds and copper concentration in the serum of hens". In EQS Environmental Quality and Safety: Global Aspects of Chemistry, Toxicology and Technology as Applied to the Environment, Vol. 3, Academic Press, NY, pp. 173-176. A study of several compounds for delayed neurotoxicity. Fenthion was found to be negative. No data. No DPR review needed. Aldous, 3/12/92.

214-044 024936 Exact duplicate of 043:010678, above.

214-044 024937 Kimmerle, G. "Acute toxicological studies for neurotoxic effect to chickens", Bayer (Wuppertal-Elberfeld), May 20, 1965. Preliminary toxicity data for dose level setting for subsequent neurotoxicity studies. No DPR review necessary. Aldous, 3/12/92.

NEUROTOXICITY, RAT

**** 214-117; 155670**; “E 1752 (Common Name Fenthion): Acute Oral Neurotoxicity Screening Study in Wistar Rats”; (M. Dreist and A. Popp; Bayer AG, Department of Toxicology, D-42096 Wuppertal, Germany; Report No. 107649; 3/20/97); E 1752 Technical Grade (fenthion, purity: 94.6%) was administered by gavage to 18 rats/sex/group at doses of 0, 1, 50 and 125 mg/kg to males and 0, 1, 75, and 225 mg/kg to females. Four females in the 225 mg/kg group died. Clinical signs included uncoordinated and spastic gait, palmospasms, tremors, chewing movements, red lacrimation, salivation, diarrhea, piloerection, decreased motility and reactivity, labored breathing, flaccidity and hypothermia. These signs were not evident in the 1 mg/kg group. Mean body weights were significantly reduced in the high dose groups of both sexes at 7 days after dosing. In the functional observational battery, both the middle and high dose groups demonstrated significant cholinergic signs, i.e., gait abnormalities, involuntary clonic motor movements, labored breathing and signs of autonomic poisoning. These signs were prominent on the day of dosing. On day 7, only open field activity was marginally increased in both sexes at 125 and 225 mg/kg, respectively. Animals in the two higher groups demonstrated decreased motor and locomotor activity on the day of dosing. These effects were still somewhat evident after 14 days. Grip strength was significantly less for the animals in the two high dose groups on the day of dosing. The effect was largely reversed by day 7. Footsplay was minimally affected by the treatment even on the day of dosing. Plasma (PChE), erythrocyte (RBC ChE) and brain (BChE) cholinesterase activities were significantly less in the two high dose male groups (PChE: both 50 and 125 mg/kg, 10.3% of control), (RBC ChE: 50, 11.1%, 125, 7.8%), and (BchE: 50, 20.3%, 125, 14.2%). Among the females, the RBC ChE and BChE activities were significantly less in the 1 mg/kg as well (RBC ChE: 78.1% of control, BChE: 91.1% of control). No treatment-related lesions were evident in the nervous tissue. **Adverse Effect** indicated: severe signs of cholinergic poisoning; **NOEL:** (M) 1 mg/kg (based on signs of cholinergic poisoning and significant cholinesterase inhibition in the 50 mg/kg group, (F) < 1 mg/kg (based on dose-related cholinesterase inhibition in the 1 mg/kg group); **NOAEL:** (M/F) 1 mg/kg (based on signs of cholinergic poisoning and significant cholinesterase inhibition in the 50 and 75 mg/kg groups, respectively. **Study acceptable**. (Moore, 9/19/97)